Scoping Document

for a Health Technology Assessment (HTA) on

Clinical Effectiveness, Safety and Cost-Effectiveness of Docetaxel, Abiraterone, Enzalutamide, Apalutamide or Radiotherapy plus Androgen Deprivation Therapy versus Androgen Deprivation Therapy Alone in Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer

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Background

The Swiss Medical Board (SMB) plans to commission a health technology assessment (HTA) in the area of cancer drugs. By addressing a specific case example of high patient-level and health system-level relevance, the HTA aims to have a two-fold impact: First, it will provide an up-to-date evaluation of the current evidence in a specific decision context, that will allow to derive treatment recommendations for patients in that situation. Second, the HTA seeks to explore current issues evolving around determining the value of novel cancer drugs and performing HTA in Switzerland in this context, and advance the area of HTA by providing additional scientific value with an impact on longer-term decision-making, HTA processes and/or value assessment in cancer care. This may include the incorporation of further elements of high current interest in HTA research, such as benefit-harm assessment or the consideration of patient preferences.

Rationale

Prostate cancer is the most frequent cancer in men, placing a high burden on patients and healthcare systems. With an age-standardized incidence of 115.7/100,000 person-years, prostate cancer is currently estimated to affect over 43,000 patients in Switzerland [1]. Prostate cancer is characterized by a relatively slow disease progression, especially when detected and treated in early, localized stages. This manifests in a relatively high 5-year survival of 88.6% after diagnosis, while the mortality rate of 22.0/100,000 person-years is still high compared to other cancer types [1]. Prostate cancer and its progression typically are androgen-dependent and respond well to treatments that reduce the production of androgens including testosterone, such as orchidectomy (i.e., surgical castration) or gonadotropin-releasing hormone agonists or antagonists (e.g. leuprolide, goserelin, degarelix). These treatments are summarized under the term androgen deprivation therapy (ADT). In recent years, substantial advances have been made in the treatment of prostate cancer, significantly improving the prognosis of patients with advanced disease.

A subject of high current scientific interest is the management of patients with newly diagnosed, metastatic, hormone-sensitive prostate cancer (mHSPC) [2–4]. Patients are typically diagnosed with mHSPC either as their initial diagnosis of prostate cancer (i.e., *de novo* mHSPC; estimated 10% of prostate cancer patients based on National Institute for Cancer Epidemiology and Registration (NICER) data), or after a relapse after local treatment of the primary tumor (i.e., progression after prior local therapy). Patients with "hormone-sensitive" disease have either not previously received ADT or have demonstrated ongoing sensitivity to ADT. An overview of patient trajectories is provided in Figure 1.

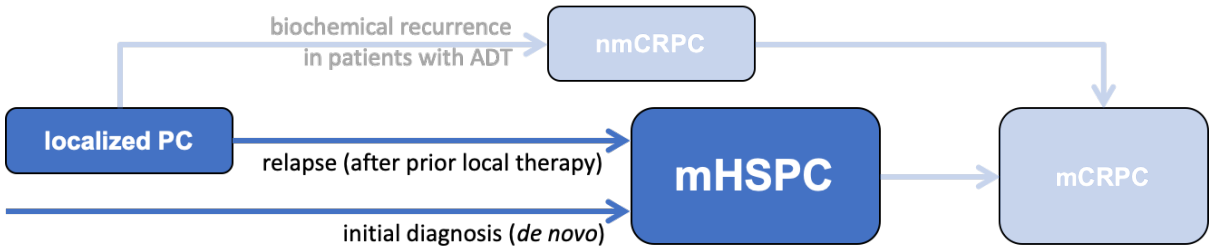

Figure 1: Overview of clinical trajectories of prostate cancer patients. Patients may be newly diagnosed with metastatic, hormone-sensitive prostate cancer (mHSPC) either as an initial diagnosis (de novo), or after a relapse after prior local therapy for localized prostate cancer (PC). Patients progressing biochemically (non-metastatic) or through metastasis under androgen-deprivation therapy (ADT) are considered to have castration-resistant prostate cancer (nmCRPC or mCRPC, respectively).

There is a therapeutic need for treating patients with mHSPC in order to prolong survival, improve or maintain quality of life, and delay disease progression. While ADT was long considered the standard of care for mHSPC patients, several different treatments are now available that have shown benefits when given in combination with ADT. These treatments include chemotherapy with docetaxel, novel hormonal treatments (i.e., second-generation anti-androgens) such as abiraterone, enzalutamide and apalutamide, as well as radiotherapy. When added to ADT, both docetaxel and abiraterone demonstrated significant effects in prolonging overall survival in long-term analyses of several trials [5–12], while one trial on docetaxel failed to show such a benefit [13,14]. Enzalutamide and apalutamide also demonstrated significant effects on overall survival in early analyses [15,16], and another trial on enzalutamide showed promising results [17]. However, the effects of some of these treatments may depend on the volume and risk category of the disease, as well as whether mHSPC was diagnosed *de novo* (i.e., as the first diagnosis) or after prior local therapy (i.e., local treatment of the primary tumor). Additionally, external beam radiotherapy to the prostate was shown to have survival benefits in the subgroup of prostate cancer patients with low disease volume, but not in the overall mHSPC population [18,19]. The optimal treatment for men with newly diagnosed mHSPC both for patients diagnosed *de novo* and relapsing after prior local therapy, is thus currently unclear and additionally depends on clinical factors and patient preferences.

Table 1: Landmark randomized controlled trials in newly diagnosed mHSPC and respective publications.

Trial name	Interventions	Publication	Publication content
GETUG-AFU 15	ADT ADT+Doc	Gravis 2013, Lancet Oncol [13]	Primary analysis of OS, PFS and QoL outcomes (mFU 50m)
		Gravis 2016, Eur Urol [14]	Long-term analysis of OS and PFS outcomes (mFU 83.9m)
CHAARTED	ADT ADT+Doc	Sweeney 2015, NEJM [5]	Primary analysis of OS and PFS outcomes (mFU 28.9m)
		Kyriakopoulos 2018, JCO [6]	Long-term analysis of OS and PFS outcomes (mFU 53.7m)
		Morgans 2018, JCO [22]	Analysis of QoL outcomes
		Gravis 2018, Eur Urol [23]	Pooled analysis of individual patient data from GETUG-AFU-15 & CHAARTED
STAMPEDE (multi-arm multi-stage platform trial)	ADT ADT+Doc	James 2016, Lancet [7] [1]	Primary analysis of OS and PFS outcomes (mFU 43m)
		Clarke 2019, Ann Oncol [8]	Long-term analysis of OS and PFS outcomes (mFU 78.2m)
	ADT ADT+Abi	James 2017, NEJM [9] [1]	Primary analysis of OS and PFS outcomes (mFU 40m)
		Hoyle 2019, Eur Urol [10]	Risk- and volume-stratified analysis of OS and PFS outcomes

	ADT+Doc ADT+Abi	Sydes 2018, Ann Oncol [24] [1]	Direct comparison for overlap between ADT+Doc and ADT+Abi arms within STAMPEDE
	ADT ADT+RTx	Parker 2018, Lancet [18] [2]	Primary analysis of OS and PFS outcomes (mFU 37m)
LATITUDE [2,3]	ADT ADT+Abi	Fizazi 2017, NEJM [11]	Primary analysis of OS and PFS outcomes (mFU 30.4)
		Fizazi 2019, Lancet Oncol [12]	Long-term analysis of OS and PFS outcomes (mFU 51.8m)
		Chi 2018, Lancet Oncol [25] [2]	Analysis of QoL outcomes
ENZAMET [4,5]	ADT+nsAA ADT+Enz	Davis 2019, NEJM [15]	Primary analysis of OS and PFS outcomes (mFU 34m)
ARCHES [4]	ADT ADT+Enz	Armstrong 2019, JCO [17]	Primary analysis of OS, PFS and QoL outcomes (mFU 14.4m)
TITAN [4]	ADT ADT+Apa	Chi 2019, NEJM [16]	Primary analysis of OS and PFS outcomes (mFU 20.5m)
		Agarwal 2019, Lancet Oncol [26]	Analysis of QoL outcomes
HORRAD [2]	ADT ADT+RTx	Boevé 2018, Eur Urol [19]	Primary analysis of OS and PFS outcomes (mFU 47m)
ARASENS [5]	ADT ADT+Daro	*study ongoing*	*Primary analysis expected 2022*
PEACE1	ADT+Doc ADT+Doc+Abi ADT+Doc+RTx ADT+Doc+Abi+RTx	*study ongoing*	*Primary analysis expected 2020*

Legend: [1] = includes non-metastatic patients; [2] = includes de novo patients only; [3] = includes high-risk patients only; [4] = includes patients with prior docetaxel; [5] = includes patients with concurrent docetaxel; Abi = Abiraterone; ADT = Androgen Deprivation Therapy; Apa = Apalutamide; Daro = Darolutamide; Doc = Docetaxel; Enz = Enzalutamide; QoL = Quality of Life; m = months; mHSPC = metastatic hormone-sensitive prostate cancer; mFu = median follow-up; nsAA = non-steroidal Anti-Androgen (first generation); OS = Overall Survival; PFS = Progression-Free Survival; RTx = Radiotherapy.

An overview of the current evidence on mHSPC treatments is given in Table 1, with further results to be expected until 2020 (within the timeframe of this HTA) [3,4]. While no direct comparisons exist for most of the treatment options, long-term data, pooled and stratified analyses are now available for docetaxel and abiraterone. To our knowledge, no comparative HTA has so far been conducted for the treatment of newly diagnosed mHSPC. The German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and the Ludwig-Boltzmann Institut (LBI) in Austria have each conducted a single-technology HTA on abiraterone and enzalutamide in newly diagnosed mHSPC, respectively. The National Institute for Health and Care Excellence (NICE) in the United Kingdom is currently conducting single-technology HTAs for abiraterone, enzalutamide and apalutamide in this context. No formal HTA is available on docetaxel in mHSPC, while NICE conducted an evidence summary in 2016. In Switzerland, only treatment abiraterone (limited to high risk mHSPC) is currently approved for use in mHSPC by swissmedic [20]. Docetaxel is commonly used *off-label* in this indication. Apalutamide is approved for use in mHSPC by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Enzalutamide is approved for use in mHSPC by the FDA and approval by the EMA is pending (as of 13 Mar 2020). Current drug prices according to the Swiss "Spezialitätenliste" are shown in Table 2. Docetaxel is available as a generic drug in Switzerland [20], while a current legal dispute over the patent on abiraterone in the United States may open the market for generic versions before formal patent expiration [21]. According to Swiss experts, radiotherapy is currently primarily performed in men with newly diagnosed mHSPC with low disease volume (or low risk) and a good overall health state. From the perspective of HTA and health system decision-making,

this makes mHSPC an important and interesting context to explore, with respect to market authorization, reimbursement decisions and drug pricing.

Table 2: Current public drug prices and swissmedic approval according to the Swiss "Spezialitätenliste".

Drug	Brand name	Dose	Extras	Approval status	Drug costs*
Docetaxel	Taxotere® (Sanofi-Aventis) *generic versions available*	75mg/m² i.v. q3w, 6 cycles	+ prednisone 10mg/d	*off-label*	517-808 CHF/cycle#
Abiraterone	Zytiga® (Janssen-Cilag)	1x1000mg/d	+ prednisone 5mg/d	approved (high risk)	3529 CHF/m
Enzalutamide	Xtandi® (Astellas Pharma)	1x160mg/d		*not yet approved*	4011 CHF/m
Apalutamide	Erleada® (Janssen-Cilag)	1x240mg/d		*not yet approved*	*not yet determined*

Legend: CHF = Swiss Francs; d = day; i.v. = intravenous; m = month (28 days); mg = milligrams; q3w = every 3 weeks. * drug costs represent public price according to Swiss "Spezialitätenliste" (www.compendium.ch; accessed 13 Nov 2019), excluding cost of prednisone or other supportive treatment. # drug cost per cycle assuming a dose of 100 to 160mg, depending on body surface area.

The treatment of mHSPC patients with a combination of ADT and older non-steroidal anti-androgens (nsAA; e.g. of the first-generation, such as bicalutamide, flutamide or nilutamide) has been an important treatment option before the development of the novel hormonal drugs. Some mHSPC patients in Switzerland may thus remain on such treatment regimen. However, according to Swiss experts, these older nsAA are no longer used in newly diagnosed patients in European health systems due to the availability of newer and more effective treatments [2]. Based on the available evidence, the additional benefits of the older nsAA in advanced prostate cancer are generally considered to be limited [27]. This HTA will thus include patients that have received first-generation anti-androgens as part of the active comparator arm, but will not evaluate such treatments separately as an experimental intervention. Furthermore, some studies have investigated the use of zoledronic acid and celecoxib as supportive treatments for mHSPC [7]. However, these therapies have not shown convincing additional benefits to chemotherapy or novel hormonal therapies and are to our knowledge not commonly used in current practice in Switzerland. Another matter of current debate is the optimal sequencing of treatments, for which randomized controlled trial (RCT) data are lacking. This HTA will, however, focus on the optimal first-line treatment in mHSPC, which also commonly determines later treatment options and is relevant for all patients with newly diagnosed mHSPC.

In summary, the decision to conduct this HTA in the specific decision context of newly diagnosed mHSPC was made for the following reasons. Prostate cancer is a relevant public health topic in Switzerland due to its high incidence and the relatively long expected survival with treatment. The treatment options available in mHSPC have changed substantially in recent years due to the development of novel and highly effective hormonal treatments, as well as emerging evidence on the effectiveness of chemotherapy in this setting. However, all these drugs also have a relevant profile of adverse effects and may incur additional costs to healthcare systems and patients. High drug prices have led to controversies in other jurisdictions regarding the approval and reimbursement of novel

hormonal drugs. The availability of evidence in this context is variable and reflects the typical situation of regulatory decision-making in cancer drugs. While data is very recent and rather limited for enzalutamide and apalutamide in mHSPC, longer-term follow-up, directly comparative and stratified data are available for docetaxel and abiraterone. This situation may allow insightful comparisons between treatments with a different availability of evidence, contrasting cancer drugs in the process of approval with longer established systemic treatments, as well as with other treatment modalities such as radiotherapy. While the available evidence is expected to increase in coming years (potentially within the timeframe of this HTA), no large changes in the therapeutic approaches are currently anticipated. Furthermore, the higher amount of available data for docetaxel and abiraterone may enhance the conduct of complementary analyses, such as benefit-harm assessment. Patient populations in studies for mHSPC are heterogenous (e.g. *de novo* vs. prior local therapy) and treatment response may be different between certain patient subgroups (e.g. low vs. high volume or risk). However, the number of such predictive subgroups may be relatively low compared to other cancer contexts, thus facilitating stratified analyses and deriving treatment recommendations. Finally, there may be a variation in practice depending on the treating physician. Some specialists may have a preference to favor one therapy over another, which may also depend on the field of practice (e.g., medical oncology or urology). For these reasons, the context of mHSPC was considered an ideal case example to provide a basis for recommendations by the SMB and make a useful contribution to the scientific literature, while also gaining experiences with and exploring pertinent issues in conducting HTA in the context of cancer drugs in Switzerland.

Objectives

The HTA aims to provide a comparative assessment of the different available systemic first-line treatments for adult men with newly diagnosed, metastatic, hormone-sensitive prostate cancer. Specific objectives include the following:

- Determine the clinical effectiveness of the different treatment options regarding overall survival, cancer-specific endpoints and health-related quality of life
- Assess adverse events and toxicity of the different treatment options
- Evaluate the cost-effectiveness and budget impact of the different treatment options
- Provide a comparative benefit-harm assessment of the different treatment options
- Examine results stratified by important subgroups, to the extent possible given data availability.

Decision Context (PICO)

Population

The primary target population of this HTA are adult men with newly diagnosed, metastatic, hormone-sensitive prostate cancer (mHSPC), both diagnosed *de novo* and relapsing after prior local therapy, that have not previously undergone systemic therapy.

Patients pre-treated with ADT alone or in combination with first-generation nsAA will be considered eligible. Patients that have received chemotherapy with docetaxel prior to the start of novel hormonal therapy will be excluded, but may be considered in secondary analyses or if data availability dictates so.

Metastatic cancer will be defined as the presence of one or more distant metastases irrespective of the extension of the primary tumor and lymphatic spread (i.e., M1 stage with any T and N stage according to the TNM classification). The term "hormone-sensitive" will be considered synonymous to the terms "castration-sensitive", "hormone-naïve" and "castration-naïve" prostate cancer. This includes both clinical scenarios in which patients have either not previously received ADT or have demonstrated ongoing sensitivity to ADT [2]. Studies including more than 10% of patients with rare forms of prostate cancer, such as aggressive variant prostate cancer (i.e., with neuroendocrine differentiation or small cell features) will be excluded. Patients with non-metastatic (M0) prostate cancer will be excluded, but may be considered in secondary analyses or if data availability dictates so.

Intervention

The following interventions will be considered eligible:

- ADT + docetaxel, intravenous chemotherapy (in combination with prednisone) followed by ADT alone
- ADT + abiraterone (in combination with prednisone), daily oral medication (licensed dose)
- ADT + enzalutamide, daily oral medication (licensed dose)
- ADT + apalutamide, daily oral medication (licensed dose)
- ADT + radiotherapy, external beam radiation therapy to the prostate followed by ADT alone

Any concurrent or protocolized immediate sequential combination of the aforementioned treatments will also be included.

Excluded interventions are:

- Bone agents (such as zoledronic acid)
- COX-2 inhibitors (such as celecoxib)

Comparator

The following interventions will be considered as comparator treatments:

- ADT alone or in combination with placebo, daily oral medication (licensed dose)
- ADT + first-generation nsAA (such as bicalutamide, flutamide or nilutamide) alone or in combination with placebo, daily oral medication (licensed dose)

ADT may involve orchidectomy or treatment with gonadotropin-releasing hormone agonists or antagonists.

Outcomes

Critical effectiveness outcomes

Overall survival

Health-related quality of life (HRQoL)

- Overall health-related QoL (e.g. EQ-5D, SF-36, EORTC QLQ-C30)
- Prostate cancer-specific QoL (e.g. EORTC QLQ-PR25, FACT-P, FACIT-F, Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI))

Important effectiveness outcomes

Progression-free survival (expressed by one of the following outcomes, whichever is judged to most closely reflect a meaningful clinical progression, either by leading to a decrease in QoL or an increase in symptoms, or to a change in treatment - in the following order of priority):

1. Clinical progression-free survival (cPFS): Time to progression in clinical symptoms or radiographic findings, or death.
2. Radiographic progression-free survival (rPFS): Time to progression in radiographic findings, or death.
3. Failure-free survival (FFS): Time to progression in clinical symptoms, radiographic findings or biochemical markers, or death.
4. Biochemical (PSA) progression-free survival (bPFS): Time to progression in biochemical markers, or death.

Safety outcomes: adverse events and toxicity

All available data on adverse events and toxicity outcomes, including severity (based on Common Terminology Criteria for Adverse Events (CTCAE)). Adverse effects may be summarized in composite outcomes, if deemed appropriate.

Health economic outcomes

Direct costs (e.g. related to resource utilization; broken down into categories)

Indirect costs (e.g. due to workdays lost)

Relevant resource use parameters

Quality-adjusted life years (QALY) gained, life-years (LY) gained

Incremental cost-effectiveness ratio (ICER; costs per QALY or LY gained)

Budget impact estimates

Study Designs

Evidence from RCTs, including multi-arm multi-stage trials, will primarily be considered in the assessment of clinical effectiveness and safety of mHSPC treatments. While observational evidence may generally be more sensitive to and more closely reflect the real-world adverse effects of prostate cancer treatments, the adverse event and toxicity profile of the systemic mHSPC treatments can be expected to be sufficiently well known in order to be adequately reflected in the RCT monitoring data. As both docetaxel and the novel hormonal agents abiraterone and enzalutamide have been studied and used for several years in other indications, it can be assumed that investigators and physicians participating in the trials were aware of and adequately sensitive to the potential harms of treatment. Evidence from observational studies and registries will be considered in the assessment of the clinical effectiveness and safety where they are judged to provide relevant additional information at limited risk of contributing to heterogeneity and bias due to study design or confounding [28].

Subgroups of Interest

In addition to the primary target population, the following patient subgroups of interest may be addressed in the HTA, depending on the available information:

- *De novo* vs. progression after prior local therapy
- High vs. low volume disease (according to CHAARTED, either of the following two criteria: visceral metastases or ≥4 bone lesions with ≥1 outside of the vertebral bodies and pelvis)

- High vs. low risk disease (according to LATITUDE, at least two out of the following three criteria: Gleason score ≥8 and/or ≥3 lesions on bone scan and/or presence of measurable visceral lesions)
- Restricted physical performance vs. unrestricted performance (ECOG Status ≥1 vs. 0).

Part I: Assessment of Clinical Effectiveness and Safety

Current Evidence and Identification of Literature

A preliminary exploratory screening of up-to-date reference literature, systematic reviews, output from the STOPCAP collaborative, existing HTA documents and conference proceedings of the Advanced Prostate Cancer Consensus Conference in September 2019 resulted in the list of trials illustrated in Table 1. In this context, it is reasonable to assume that the relevant evidence is captured via these sources. Meanwhile, for the assessment of the clinical effectiveness and safety of mHSPC treatments, a more systematic literature review will be conducted.

Systematic Review of the Literature and Study Selection

A systematic review of the literature will be performed to identify eligible RCTs in the context of mHSPC. A targeted systematic search in PubMed (MEDLINE) will be conducted for systematic reviews and meta-analyses published between January 2016 and the date of search. Potentially eligible references in these systematic reviews will then be collected and the list of excluded studies will be screened. In this context, all relevant RCTs are assumed to be covered by these systematic reviews. A strong basis is the STOPCAP initiative, a collaborative project aiming to synthetize the latest evidence using a framework for adaptive meta-analysis in mHSPC [29]. A follow-up search for RCTs published after the last search date of the most recent systematic review will be conducted in the MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify further relevant studies, as well as to identify more recently published trial data. Search terms will include "prostate cancer", "hormone-sensitive" (and synonyms), "docetaxel", "abiraterone", "enzalutamide", "apalutamide" and "radiotherapy". An RCT-specific search filter will be applied [30]. This search will be complemented with references retrieved from most recent international conference proceedings (e.g. European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), Advanced Prostate Cancer Consensus Conference (APCCC), European Association of Urology (EAU), American Urological Association (AUA)), lists of publications related to the identified RCTs in clinical trials registries (e.g. ClinicalTrials.gov), and the screening of recent overview articles and editorials. Furthermore, experts will be contacted for the identification of additional relevant references.

In a first selection step, the identified references will be screened based on title and abstract to identify potentially eligible records and relevant RCTs. In a second step, potentially eligible records will be screened in full-text to assess eligibility. Eligible records will be grouped and linked to eligible RCTs. Screening and eligibility assessment will be conducted by two independent reviewers, and conflicts will be resolved by consensus with the consultation of a third reviewer.

A more detailed protocol for the systematic review and network meta-analysis will be developed and registered on PROSPERO. The systematic review will be reported in line with PRISMA guidelines and their extension for network meta-analyses [31,32].

Data Extraction and Quality Assessment

Data extraction will be conducted across different publications related to the same trial. Data related to the study design and setting, sample size, study participant characteristics and inclusion criteria, experimental intervention(s), (active) comparator intervention(s), reported primary and secondary outcomes, reported safety outcomes, effect measures, and median time of follow-up will be collected. Study results will be extracted based on reported intention-to-treat data. Where available, stratified subgroup-specific results will be collected.

The risk of bias of eligible studies will be assessed using the revised Cochrane Risk of Bias tool for RCTs (RoB 2) across the domains of randomization, deviations from protocol, missing outcome data, outcome measurement and reporting of results [33]. Outcome-specific assessment will be conducted for the critical outcomes specified for this review only.

Data extraction and risk of bias assessment will be performed independently by two reviewers, with the consultation of a third reviewer for the resolution of disagreements.

Data Analysis and Synthesis

A network meta-analysis will be conducted for all crucial and important outcomes, if possible. Whether this is feasible for failure-free survival will depend on the definitions of this endpoint in the different trials and the judged adequacy of combining their results in a network meta-analysis. Results will be reported as hazard ratios (HRs) or mean differences (MDs). A preliminary network diagram is shown in Figure 2. The transitivity assumption will be assessed by analyzing details of the trials' PICOs using epidemiological reasoning. In addition, appropriate statistical tests for transitivity and consistency will be performed. Fixed-effects meta-analyses will be conducted for each direct

comparison and random-effects results will be presented where between-trial heterogeneity is judged moderate or higher (see below). Estimated results for all indirect comparisons will be presented wherever possible. Statistical adjustment for potential effect modifiers contributing to study heterogeneity (i.e., intransitivity) may be undertaken if deemed appropriate. An analysis pooling effects for different drug classes may be considered for certain outcomes to increase statistical power, depending on data availability and if judged appropriate. Heterogeneity will be assessed using the I^2 statistic. Differences in populations in terms of treatment prior inclusion (duration of ADT, prior use of docetaxel, *de novo* vs. prior local therapy), baseline morbidity (age, ECOG status), disease volume and risk category (metastatic burden, Gleason score), comparator intervention (use of ADT combined with first-generation nsAA therapy), subsequent second line treatments, and study-level risk of bias will be considered as *a priori* explanatory variables for heterogeneity. Publication bias will be assessed using funnel plots as well as appropriate statistical tests (e.g. Egger's or Peter's tests). Furthermore, we will analyze and discuss the impact of subsequent treatments after progression (i.e., treatment sequencing) on the results.

A more detailed statistical analysis plan will be developed and published in the protocol prior to the start of data collection. All analyses will be performed using R (latest program version).

Sensitivity Analyses

Sensitivity analyses will be conducted where deemed appropriate. A priori sensitivity analyses may be prespecified in a more detailed research protocol.

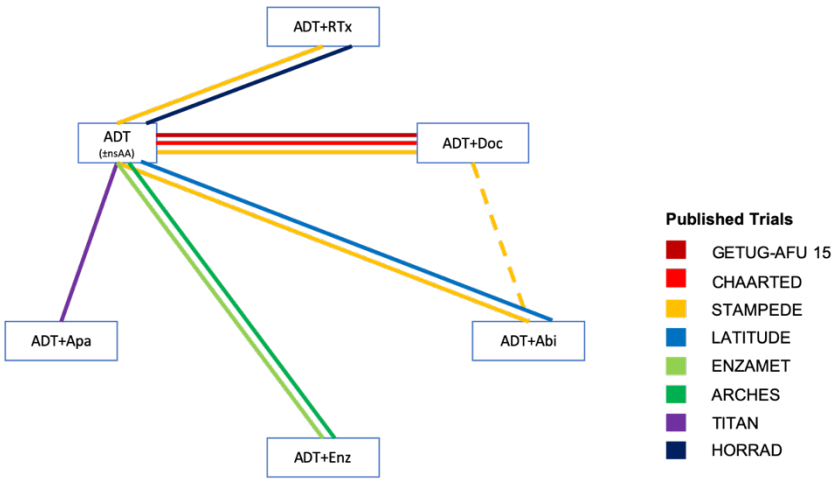

Figure 2: Preliminary network diagram of the currently published evidence for the network meta-analysis on overall survival of different treatment options in newly diagnosed mHSPC.

Assessment of the Quality of Evidence

The confidence in the available evidence will be assessed according to the GRADE approach for network meta-analyses [34]. The assessment will be conducted for all critical outcomes individually and presented in a standardized summary of findings (SoF) table.

Part II: Health Economic Evaluation

Pre-review of the health economic literature

As part of the scoping process, a preliminary search for health economic literature was conducted in PubMed (MEDLINE) to gain a first understanding of potentially relevant studies in mHSPC (e.g. cost-effectiveness, cost-utility, or cost studies). The following search strings were combined:

- Docetaxel OR Abiraterone OR Enzalutamide OR Apalutamide (N=17,665)
- Prostate cancer (N=167,199)
- Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic analyses OR Pharmacoeconomic analysis OR Price$ OR Socioeconomic$ (N=167,199)

The search conducted on 10 September 2019 resulted in 205 hits. Among them, 11 potentially relevant cost-effectiveness analyses published between 2017 and 2019 were identified. No HTA including health economic analyses on this specific PICO was captured by this search. A separate search for HTAs in PubMed and on websites of the 18 major international HTA agencies identified two single-technology HTA by IQWiG for abiraterone and by LBI for enzalutamide in mHSPC. Both only provided cost estimates without an evaluation of cost-effectiveness and are thus not included in the overview below.

Brief overview of the identified cost-effectiveness analyses

A summary of the identified cost-effectiveness analyses is provided in Table 3. As defined in the PICO, all studies included mHSPC patients (one study provided information on both mHSPC and high-risk non-metastatic prostate cancer patients). The first four studies listed in Table 3 compared abiraterone and docetaxel with antigen deprivation therapy (ADT). The other seven studies compared docetaxel with ADT. Four studies were conducted in China (including Hong Kong), three in North America, two

in Brazil, and two in Europe. Most of the analyses were conducted using a Markov model. However, model structures (e.g. types of input variables considered and assumptions), time horizons, and perspectives were very different across studies. Assuming a cost-effectiveness threshold of CHF100,000 per QALY gained, the identified studies suggest that docetaxel plus ADT is cost-effective if compared to ADT alone (the ICERs ranged from CHF2,470 to CHF50,075 per QALY gained). In contrast, abiraterone plus ADT was cost-effective if compared to ADT alone in only one study, whereas it was never cost-effective compared to docetaxel plus ADT.

Table 3: Main characteristics of the identified health economic studies in mHSPC.

Author **Country** **Population**	**Intervention vs.** **Comparator**	**Main results ***	**Model type** **Time horizon** **Perspective**
Aguiar et al. 2019 [35] Brazil mHSPC	ADT+Doc or ADT+Abi vs. ADT alone	ICER Doc+ADT vs. ADT: CHF 32,830/QALY(CE) ICER Abi+ADT vs. ADT: CHF81,184/QALY(CE) ICER Abi+ADT vs. Doc+ADT: CHF140,284/QALY (non-CE)	Descriptive analytical model 7 years NR
Chiang et al. 2019 [36] Hong Kong mHSPC	ADT+Doc or ADT+Abi vs. ADT alone	ICER Doc+ADT vs. ADT: CHF14,282/QALY (CE) ICER Abi+ADT vs. Doc+ADT: CHF358,557/QALY (non-CE)	Markov model Lifetime Societal
Ramamurthy et al. 2019 [37] USA mHSPC	ADT+Doc or ADT+Abi vs. ADT alone	ICER Doc+ADT vs. ADT: CHF50,075/QALY (CE) ICER Abi+ADT vs. Doc+ADT: CHF1,001,733/QALY (non-CE)	Markov model 3 years US-payer
Sathianathen et al. 2019 [38] USA mHSPC	ADT+Doc or ADT+Abi vs. ADT alone	ICER Doc+ADT vs. ADT: CHF34,438/QALY (CE) ICER Abi+ADT vs. ADT: CHF292,795/QALY (non-CE)	Markov model Lifetime Healthcare
Aguiar et al. 2017 [39] Brazil mHSPC and high-risk nmPC	ADT+Doc vs. ADT alone	ICER mHSPC: CHF2,757/QALY (CE) ICER high-risk nmPC: CHF25,718/QALY (CE)	Descriptive analytical model NR NR
Beca et al. 2019 [40] Canada mHSPC	ADT+Doc vs. ADT alone	ICER: CHF24,027/QALY (CE)	Markov model 15 years payer
Garcia de Paredes et al. 2017 [41] Spain mHSPC	ADT+Doc vs. ADT alone	ICER: CHF2,470-4,196/LYG (CE)	NR # NR NR
Liu et al. 2019 [42] China mHSPC	ADT+Doc vs. ADT alone	ICER: CHF9,487/QALY* (CE)	Markov model Lifetime healthcare
Woods et al. 2018 [43] UK mHSPC	ADT+Doc vs. ADT alone	ICER: CHF6,742/QALY (CE)	Markov model Lifetime Healthcare
Zhang et al. 2017 [44] China mHSPC	ADT+Doc vs. ADT alone	ICER: CHF38,657/QALY (CE)	Markov model 20 years Societal
Zheng et al. 2017 [45] China mHSPC	ADT+Doc vs. ADT alone	ICER: CHF26,498/QALY (CE)	Markov model 10 years Societal

Legend: Abi=Abiraterone, ADT=Androgen Deprivation Therapy, CE=Cost-Effective (assuming a cost-effectiveness threshold of CHF100,000 per QALY gained), Doc=Docetaxel, ICER=Incremental Cost-Effectiveness Ratio, mHSPC=metastatic Hormone-Sensitive Prostate Cancer, nmPC=non-metastatic Prostate Cancer, NR=Not Reported, QALY=Quality-Adjusted Life Years, vs.=versus. *Following exchange rates were used: CNY1=CHF0.14, €1=CHF1.09, R$1=CHF0.24, £1=CHF1.22, USD1=CHF0.99. #Note: the paper is a summary of a Doc evaluation report by GENESIS-SEFH. The original document, probably in Spanish, was not found.

Approach to health economic assessment

The preliminary literature search in PubMed led to the identification of several cost-effectiveness analyses investigating docetaxel or abiraterone. In contrast, there was no cost-effectiveness study on enzalutamide nor apalutamide (presumably because they are the most recent compounds, for which long-term results are not yet available). Based on the pre-scoping and the pre-review of the health economic literature, the following approaches are suggested:

Full systematic search

In a full systematic literature search, literature on the cost-effectiveness of abiraterone, enzalutamide, apalutamide, and docetaxel in patients with metastatic hormone-sensitive prostate cancer will be identified. The identified economic studies will be critically assessed. As one tool, the “Consolidated health economic evaluation reporting standards” (CHEERS) checklist will be used [46]. Plausibility of the results and the transferability of international results to Switzerland will be critically considered. Transferability will be assessed through a multistep approach based on previously published procedures [47–50]. To the extent that they are transferable, costs and incremental cost-effectiveness ratios (ICERs) may be adapted to Switzerland by taking into account differences in healthcare resource utilization and purchasing power parities [51,52]. Change of healthcare costs over time will be used in this case to extrapolate all cost estimations to the same year (presumably 2018) [53]. The aim of the cost adaptation would be to make international cost-effectiveness results more comparable and to achieve a rough indication of the possible magnitude of ICERs for Switzerland. It will not be possible to directly interpret resulting estimates as "ICERS for Switzerland", where practice patterns and effects may differ from those published internationally.

Results will be summarized in tabular and/or graphical formats and synthesized narratively.

Cost-effectiveness analysis

Ideally, a *de novo* cost-effectiveness analysis will be conducted for Switzerland including all treatments listed in the PICO. This analysis would adopt a lifelong time horizon if possible, although limited data would imply a need for extrapolation. The results of the pre-review of the economic literature suggest that long-term data should be available for abiraterone and docetaxel (i.e. cost-effectiveness analyses using a lifetime horizon have already been published). In contrast, there are currently no cost-effectiveness analyses for enzalutamide nor apalutamide respecting the PICO.

To correctly compare the selected interventions, it is important to apply the same time horizon. Depending on the available literature and on the results of the network meta-analysis conducted, the following approaches may be pursued:

- Markov model with lifetime horizon if long-term data are available for all interventions (or if long-term estimations, especially for enzalutamide and apalutamide, are available)
- Markov model with shorter time horizon based on the data available plus long-term modelling based on extrapolation of long-term estimates
- Alternative approaches may include health economic evaluation based on a partitioned survival model, depending on the type of evaluation judged more adequate for the decision context and better comparable to other health economic studies in the context.

Budget impact analysis

The actual expenditure for the treatment of mHSPC patients and the impact on the Swiss healthcare system will also be investigated in a budget impact analysis, considering the available information for Switzerland. A base case scenario assuming mHSPC treatment with ADT alone will be compared with scenarios including docetaxel, abiraterone, enzalutamide and apalutamide (assuming different market shares).

It is important to emphasize that the range and complexity of the health economic analyses will depend on the results of the systematic reviews. Only after assessing the quantity and quality of the available information will it be possible to judge whether a full analysis/adaptation of international cost-effectiveness analyses and/or a detailed *de novo* cost-effectiveness analysis are most sensible to perform.

Perspective

Costs will be assessed from a health insurance law (KVG) perspective as well as from a societal perspective.

Additional data sources

In addition to the published literature, the following sources of information may be used for the cost and budget impact analyses:

- Data from NICER will be used to investigate incidence, prevalence, mortality, and survival of patients with prostate cancer (and, if possible, of those with mHSPC) [1]

- Swiss specialty list: will be used for the drug prices [20]
- Swiss Hospital Statistics 2016 (and 2017/2018, if available): patients with prostate cancer will be identified through relevant treatments (e.g. CHOP codes), diagnostic codes (i.e. ICD-10 codes), and hospitalization codes (i.e., SwissDRG codes) [54]
- Diagnosis-related case cost statistics (Statistik diagnosebezogener Fallkosten) of the Swiss Federal Office of Statistics: this statistic may be used to estimate the hospitalization cost per patient according to their SwissDRG (i.e., according to their diagnoses and treatment combinations received) [55].
- Swiss tariff framework for ambulatory care (TARMED): TARMED positions may be used to estimate costs of outpatient consultations, services and interventions provided [56].

Further sources may be identified and added at a later point in time.

Part III: Benefit-Harm Assessment

For the assessment of novel drugs and technologies, it is highly important to balance the expected benefits against the potential harms. Quantitative benefit-harm assessment (BHA) provides a means to explicitly, systematically and transparently assess the benefit-harm balance, while taking the baseline risks and preferences of patients into account and exploring uncertainty in the decision scenario. To our knowledge, no quantitative BHA has yet been conducted for cancer treatments in mHSPC or in the area of advanced prostate cancer more generally. Important initiatives by various HTA agencies and international collaboratives are currently ongoing aiming to integrate BHA in HTA processes, in an effort to make judgement about the balance of benefits and harms of novel treatments explicit and transparent [57,58]. This may provide a significant addition to current HTA processes when it comes to determining the value of novel cancer drugs. While more experience is still needed with different methodological approaches and the incorporation of patient preferences in this context, various methods for BHA have already been established and it has become clear that the incorporation of structured and transparent BHAs is highly important for HTA. Thus, if feasible in any way, we will integrate a quantitative BHA in this HTA. A detailed rationale for conducting a BHA as part of this HTA is provided in a supplement to this scoping document (dated 17 Dec 2019).

Benefit-Harm Assessment Methodology

The available treatment options in mHSPC will be compared based on their estimated balance of benefits (i.e., clinical effectiveness) and harms (i.e., adverse effects and toxicity). The BHA will follow the recommendations outlined by the PROTECT group for the conduct of BHAs [59].

A quantitative BHA approach will be applied using mathematical modeling, as considered feasible and appropriate given the available data. A priori, we plan to use a modification of the approach published by Gail et al. [60], with which our group has substantial experience [61–64]. This model is based on an estimation of the expected absolute difference in the occurrence of each type of benefit and harm event between the two comparison groups over a defined time horizon. It thus combines evidence on the baseline risks of patients with evidence on relative treatment effects (e.g. derived from network meta-analyses). Absolute risk differences for each type of benefit and harm outcome risks are then weighted individually based on the respective relative preferences of patients towards those outcomes. The sum of the weighted harms is subtracted from the sum of the weighted benefits to provide a measure of the benefit-harm balance as a single comparison metric, the *Gail Index* (see Formula below, where *B = benefits, H = harms, w = preference weights and ARD = absolute risk difference over specified time horizon*). A positive *Gail Index* thus indicates a *net clinical benefit* of one intervention over its comparator.

$$Gail\ Index = \sum_{i=1}^{n_B} w_{B_i} \times ARD_{B_i} - \sum_{i=1}^{n_H} w_{H_i} \times ARD_{H_i}$$

In order to take uncertainty about the parameter estimates used in the model into account, a probabilistic modeling approach using *Monte Carlo* simulation will be applied. Therein, parameter estimates are not treated as fixed values, but assigned prior distributions from which parameters are sampled repeatedly, with the *Gail Index* being calculated for each iteration. As a result, a simulated probability distribution of the benefit-harm balance will be derived. This will ultimately allow a calculation of the probability with which one treatment is superior to another in terms of the benefit-harm balance for each treatment comparison.

Evidence used for the BHA will include findings from the assessment of the clinical effectiveness and safety within this HTA (Part I), as well as additional information from various sources (e.g. international literature, or registry or cohort data from Switzerland). To ensure the inclusion of the most valid and precise information in the context of mHSPC in Switzerland, evidence will be selected according to the framework provided by Fain et al. [65]. Further inputs from Swiss experts, important stakeholders and patients may be sought if necessary. Benefit and harm outcomes will be weighted through the use of estimated relative preferences from a patient perspective based on international literature and potentially the results of a preference study conducted in Switzerland (see below). The time horizon of the analysis will be chosen based on typical life-expectancy (i.e., median survival) and what is

deemed a sensible time horizon for decision-making in practice. If appropriate, additional sensitivity analyses will be conducted to explore the impact of time horizon and further model assumptions.

Complementary Elements

In parallel to this HTA, a separate study on patient preferences of mHSPC patients in Switzerland regarding the benefits and harms of the different treatments is currently planned to be undertaken in 2020. The preference study will be independent from this HTA in terms of conduct and funding. However, if feasible within the timeframe of this HTA, the results of the preference study may be used to inform parts of this HTA, especially the quantitative BHA.

Expected Impact and Public Health Relevance

This HTA will provide an up-to-date assessment of the published evidence on the systemic cancer drug therapies available for the treatment of men newly diagnosed with mHSPC. The evaluation of the clinical effectiveness and safety will take a patient-centered perspective and focus on outcomes that are relevant to patients and about which knowledge is necessary for making personalized decisions in clinical care. By evaluating the clinical effectiveness, and benefit-harm balance of docetaxel, abiraterone, enzalutamide, apalutamide, radiotherapy, as well as their combinations, it will provide additional analytical evidence that may support clinicians in making specific treatment recommendations for patients facing mHSPC treatment. By simultaneously addressing the cost-effectiveness and balance between benefits and harms of treatments, the project will give further important insights that will enable regulatory and reimbursement decision-makers to make judgements about the value of novel mHSPC treatments to patients and the healthcare system. Therefore, this project is expected to provide significant value to patients, guideline developers and decision-makers at a health system-level.

Furthermore, this HTA will be the first conducted by the SMB in the area of cancer drugs and the first to our knowledge to conduct a comparative assessment of multiple treatments in mHSPC. Thereby, this project will provide a valuable addition to the HTA landscape in prostate cancer, as well as a highly important experience with conducting HTAs in this highly sensitive context in Switzerland. The findings of this HTA will provide complementary evidence that may be highly relevant in light of upcoming regulatory and reimbursement decisions on novel and established treatments for mHSPC in Switzerland, as well as future pricing negotiations in this context.

On a methodological level, this HTA will be one of the first in the area of cancer drugs attempting to include a benefit-harm assessment in assessment process. If feasible within the timeframe of this HTA, this process will be complemented and informed by a separate, concomitant study on patient preferences in advanced prostate cancer. This study will yield important information needed to weigh the expected benefits against the possible harms of treatment and to draw better and more patient-relevant conclusions. Both the inclusion of benefit-harm assessment and the consideration and incorporation of patient preferences are currently crucial areas of research in HTA, with multiple HTA agencies and international collaboratives undertaking strong efforts in advancing this field [57,58]. Therefore, this project has a significant potential to importantly contribute to methodological developments in the area of HTA more generally.

Timeline & Milestones

Timeline and milestones for this HTA are currently planned as follows:

Termin	Meilenstein	Akteure
Scoping		
13.08.2019	Auftrag für Scoping	SMB Trägerschaft
12.08.2019	Stakeholder-Meeting	SMB Trägerschaft, Assessment Team, Krebsforschung Schweiz
20.09.2019	Entwurf Scoping-Dokument und Projektpräsentation	Assessment Team
23.10.2019	Stakeholder-Review des Entwurfs	Externe Stakeholder, SMB Expertenrat, Wissenschaftliches Sekretariat
15.11.2019	Anpassung des Scoping-Dokuments	Assessment Team
05.12.2019	Genehmigung des Scoping-Dokuments und Auftrag für Assessment	SMB Trägerschaft
Assessment		
29.05.2020	Systematischer Review und Network Meta-Analyse	Assessment Team, Externe Experten
19.06.2020	Gesundheitsökonomische Evaluation	Gesundheitsökonomie, Externe Experten
tbd	Benefit-Harm Assessment	Assessment Team, Externe Experten
03.07.2020	Entwurf Assessment-Bericht	Assessment Team, Gesundheitsökonomie
24.07.2020	Externer Review Assessment-Bericht	Externe Reviewer
15.08.2020	Revision Assessment-Bericht	Assessment Team
10.09.2020	Stakeholder Review Assessment Bericht	Externe Stakeholder
18.09.2020	Stakeholder-Konsultation	Externe Stakeholder, SMB Expertenrat, Assessment Team
21.10.2020	Übersetzung (D/F) der Zusammenfassung	Assessment Team
30.10.2020	Abgabe Assessment Bericht	Assessment Team
Finalisierung		
	Diskussion und Erstellung Bericht	Appraisal Komitee
15.01.2021	Finalisierung Bericht	Appraisal Komitee / SMB

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